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*Review Article*

# Regulatory role of long non-coding RNAs during reproductive disease

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**Abstract:** Long non-coding RNA (lncRNA) is a group of RNAs with broad biogenesis, which are longer than 200 nt and highly conserved in their secondary and tertiary structures. lncRNA that broadly participates in varied physiological processes in organisms has abundant biological function and can regulate expression of target genes at transcriptional, post-transcriptional and epigenetic levels. LncRNAs can also affect the development of diseases, and therefore be used to diagnose and treat diseases. With new sequencing and microarray techniques, hundreds of lncRNAs involved in reproductive disorders have been identified, but their functions in these disorders are undefined. In this paper, we reviewed the studies on how lncRNAs participate in the development of reproductive disorders, hoping our outcome can instruct the future study and provide new biomarkers and therapies for reproductive disorders.

**Keywords:** LncRNA, cumulus cell, placentation, Neat1, Hotair, Malat1, Mrh1, HongrES2, Pcat1, Schlap1, reproductive diseases

## Introduction

In human, over 70% of genome is continuously transcribed. In fact, only 1%-2% of the genome are coding genes, while 80%-90% non-coding regulatory elements are transcribed into long non-coding RNAs (LncRNA) [1]. The remaining are non-coding RNAs (ncRNAs). NcRNAs, including siRNA, miRNA (microRNA), piRNA (piwi-interacting RNA) and lncRNA, play an important role in spermatogenesis and female reproduction [2]. MiRNAs, a class of endogenous non-coding single stranded RNAs of about 21-25 nt, can degrade target mRNAs or inhibit their translation, and thus regulate the differentiation of target mRNAs [3]. PiRNAs, a large class of small RNAs that are 24-32 nt in length, can interact with Piwi proteins without dicer enzyme [4]. NcRNAs have been long thought as transcriptional noise because they lack biological functions [5]. LncRNAs regulate the expression of target genes at transcriptional and post-transcriptional levels [6, 7]. LncRNAs are polyadenylated and catalyzed by RNA polymerase II, and can perform various biological functions in nuclei and cytoplasm [8]. With the introduction of high-throughput sequencing, thousands of lncRNAs have been identified, characterized and categorized.

According to its position with neighboring protein-coding genes, lncRNAs can be classified as: (I) stand-alone lncRNAs; (II) natural antisense transcripts; (III) pseudogenes; (IV) intronic transcript; (V) divergent transcripts, promoter-associated transcripts, and enhancer RNAs (**Figure 1**) [9]. According to their function, lncRNAs can be classified into four categories [10, 11]: (I) signal molecule (II) decoy molecule (III) guide molecule (IV) scaffold molecule (**Figure 2**). LncRNAs participate in the proliferation, differentiation, and self-renewal of stem cells, including embryonic stem cells, induced pluripotent stem cells, and spermatogonial stem cells (SSCs). Infertility has become a global concern. Due to environmental deterioration, food crisis,

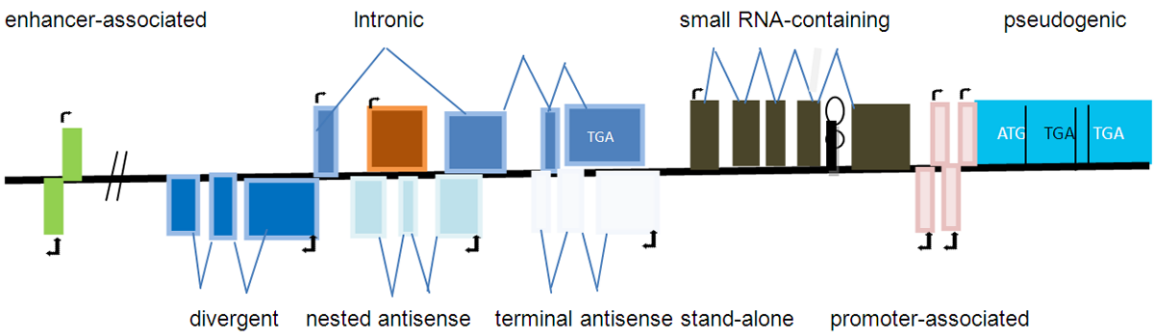


**Figure 1.** Structural classification of lncRNAs. LncRNAs may be stand-alone transcription units, or they may be transcribed from enhancers, promoters, or introns of other genes; from pseudogenes; or antisense to other genes with varying degrees of overlap, from none, to partial, to complete. lncRNAs may also host one or more small RNAs within their transcription units (Image from [9]).

electromagnetic radiation, and even life stress, the incidence of human infertility is on the rise [12, 13], mainly in developed countries.

A complex disease can be defined when: first, it is related to two different genomes (oocyte and sperm qualities are two major factors determining reproductive success), depends on endometrium receptivity [14]. The embryonic genesis, fertilization and implantation are regulated by complex biological pathways involving many molecules (such as mRNAs, non-coding RNAs, and proteins), which makes the disease more complicated. In female game to genesis, oocyte competence develops through complex processes beginning with embryonic formation and ending with MII oocyte ovulation [15]. During ovulation, the oocyte is enclosed into a lineage of ovarian somatic cells and pre-granulosa cells, and then grows into a primordial follicle [16]. The primordial follicle pool, an embryonic product of most mammal species including human, represents the female's ovarian reserve [17]. So, the embryo quality is mainly decided by the competence of the oocyte selected for fertilization. This competence is also affected by the oocyte's follicular environment [18]. However, these lncRNAs have a series of functions and participate in the development of many diseases [19-21], including cervical cancers, and neurodegenerative diseases. Recently, some lncRNAs have been found associated with preeclampsia [22-24].

In 2014, global transcriptome profiles of the samples (Compact cumulus cells) were obtained using state-of-the-art RNA sequencing techniques. G.M. Yerushalmi *et al.* identified 1746 differently expressed genes of compact and expanded CCs. Most of these genes were involved in cellular growth and proliferation, movement, cycles. Out of the DE genes, Yerushalmi *et al* found 89 long ncRNAs, 12 of which are encoded within introns of genes involved in granulosa cell processes. Analysis of these genes help identify genes and ncRNAs potentially involved in COC (cumulus oocyte complexe) maturation and cumulus expansion [25].

### LncRNA *Neat1, Malat1, Mrh1, HongrES2,* narcolepsy candidate-region 1 gene expression in male reproduction

SSCs differentiate into sperms through spermatogenesis that involves genes such as Bcl6b, Etv5, Kit L, and EPCAM. Neat1, a 3.2 kb lncRNA, forms paraspeckles and, along with other RNA complexes, modifies the transcript of coding genes [26]. In 2012, Nakagawa found that Malat1 (a type of lncRNA) was embedded in the subnuclei of mouse embryonic fibroblasts, and with pre-mRNA regulated many biological processes, such as the growth of synapses and change of cellular cycles [27, 28]. In 2014, Hu yuan, et al. found that Neat1 was expressed in rat testicular tissues and GC-I cell lines. After the injection of lentiviruses, testicular indexes (testicular weight/experimental weight ×100%) in the experimental group rose, but not significantly. At the same time, the proportion of seminiferous tubules harboring sperms dropped to 86%, indicating that Neat1 regulated rat spermatogenesis [29].

With a length of 2.4 kb, Mrhl is a type of single-axonlncRNA encoded by the nuclear genome and expressed in testes [30]. In 2008, Ganesan

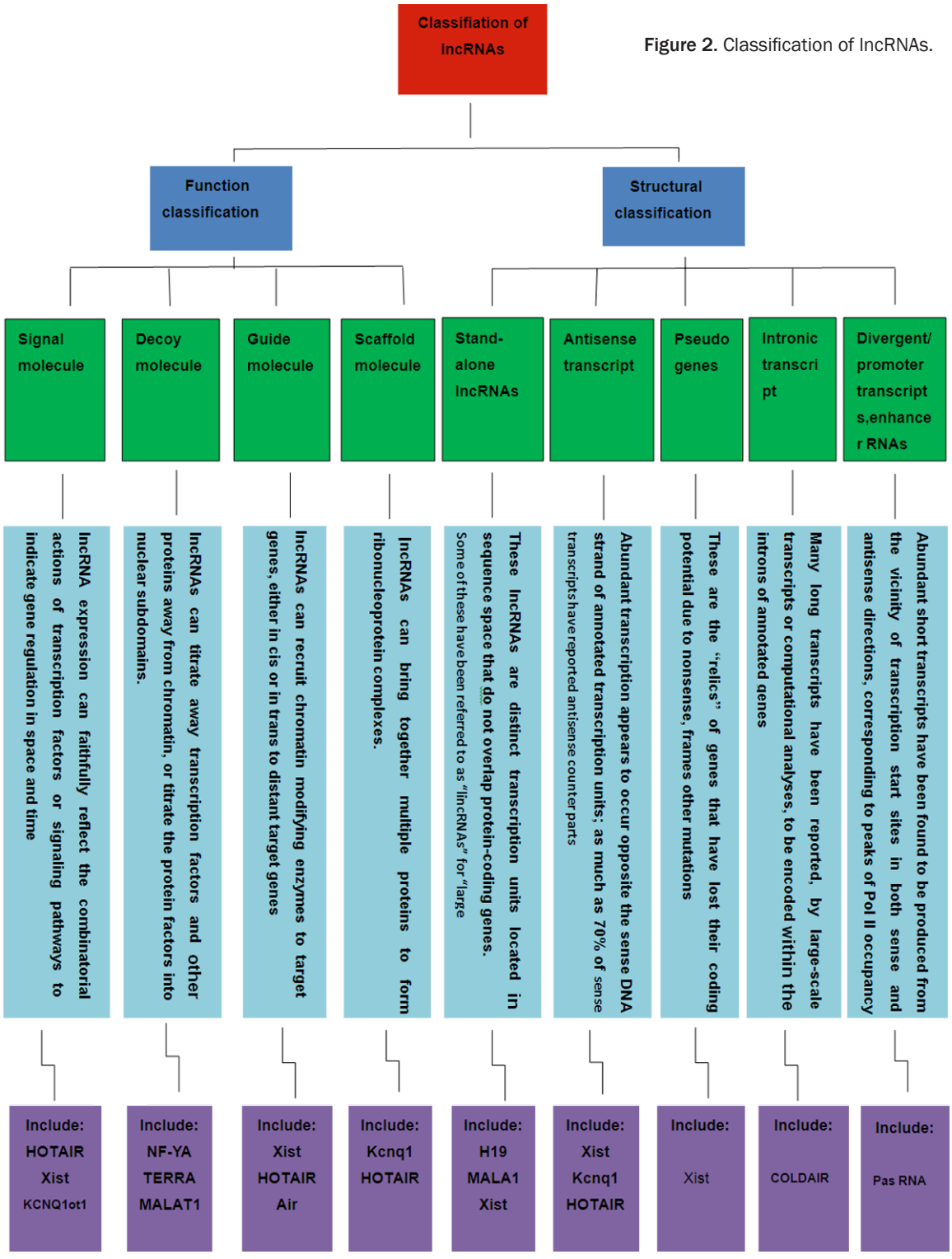


**Figure 2.** Classification of lncRNAs.

and Rao found that Mrhl regulated spermatogenesis through two molecular mechanisms. First, Mrhl is divided by Drosha into a midbody of 80 nt. These RNAs are located in the nuclei of GC1 spermatogonial lines, probably interacting with chromatin [31]. Second, Wnt is critical to mammalian spermatogenesis [32]. Cooperating with p68, Mrhl shows its negative regulation in Wnt signal. Knockdown of Mrhl expression in GC-1 SPg cell line can disrupt the expres-

**Table 1.** LncRNAs expression in reproductive diseases

| LncRNA | Length | Chromosomal location | Functions |
|---|---|---|---|
| Neat1 | 3.2 kb | 11q13.1 | Corpus luteum formation and pregnancy maintenance [29] |
| Mrh1 | 2.4 kb | Chromosome 8 | Wnt signaling regulation in spermatogonial cells; spermatogonial division and differentiation [32] |
| HongrES2 | 1588 bp | Chromosome 5 and 9 | Space-time specificity in spermatogenesis; sperm maturation [34] |
| PCAT1 | 2.0 kb | 8q24 | PCAT-1 promotes prostate cancer cell proliferation through cMyc [37, 38] |
| Schlap1 | 1.5 kb | 2q31.3 | The high expression of SCh LAP1 in Prostate tumors [39] |
| PCGEM1 | 1603 nt | 2q32.3 | Prostate tissue-specific and prostate cancer-associated [41] |
| RNAsGtl2 | 1.6 kb | 14q32.2 | Human early-stage embryonic development; oocyte maturation; zygotic genome activation [42] |
| AK124742 | 6078 bp | 3p14 | Oocyte maturation and embryo development [45] |
| LncRNA274 | --- | --- | Cytoskeletal organization and oocyte polarity in Xenopus [46] |
| XIST | 19296 nt | Xq13.2 | X-chromosome inactivation [52] |
| H19 | 2322 nt | 11p15.5 | Up-regulationin most ovarian cancer tissues compared with adjacent non-tumor samples with a significantly positive correlation between its expression and tumor stages and tumor size [55-58] |
| HOTAIR | 2377 nt | 12q13.13 | Tumorigenic factor and biomarker in various cancer types; the most investigated lncRNA in cervical cancer [61-66] |
| MALAT1 | 8708 nt | 11q13.1 | Tumor pathogenesis [67], high levels of MALAT1 in endometrioid endometrial cancer [68] |

Note: ---, Not retrieved. NEAT1: Nclear paraspeckle assembly transcript 1; Mrh1: Miotic recombination hot spot locus; Mil-HongrES2: a1.6kb mRNA-like precursor that gives rise to a new microRNA-like small RNA; Neat AK124742: A newly detected lncRNA that was identified as being natural antisense to PSMD6 and involved in oocyte maturation and embryo development; LncRNA274: A specifically high expressed in ovary; Xist: X chromosome inactive-specific transcript; H19: Imprinted maternally expressed transcript; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; HOTAIR: HOX transcript antisense RNA; PCAT1: Prostate cancer-associated transcript 1; PCAT1: Prostate cancer-associated transcript 1; Schlap1 : second chromosome locus associated with prostate-1.

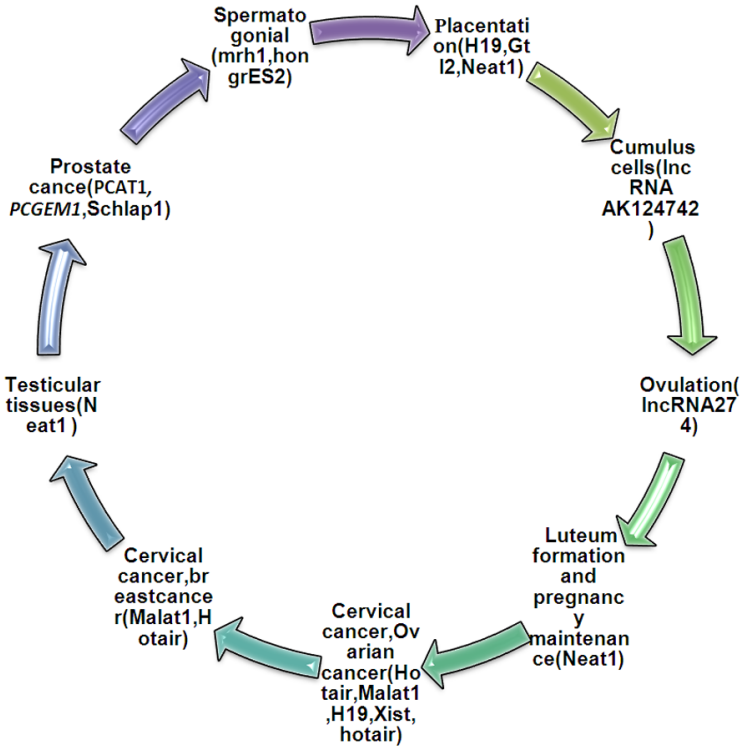


**Figure 3.** Different expression of lncRNA build up a regulatory system in reproductive diseases. NEAT1: Nclear paraspeckle assembly transcript 1; Mrh1: Miotic recombination hot spot locus; Mil-HongrES2: a1.6kb mRNA-like precursor that gives rise to a new microRNA-like small RNA; Neat AK124742: A newly detected lncRNA that was identified as being natural antisense to PSMD6 and involved in oocyte maturation and embryo development; LncRNA274: A specifically high expressed in ovary; Xist: X chromosome inactive-specific transcript; H19: Imprinted maternally expressed transcript; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; HOTAIR: HOX transcript antisense RNA; PCAT1: Prostate cancer-associated transcript 1; PCAT1: Prostate cancer-associated transcript 1; Schlap1: second chromosome locus associated with prostate-1.

sion of genes that are responsible for cell signal transduction and development. Most of these genes are members of the Wnt signaling pathway promoting cell differentiation and inhibiting cell growth. Therefore, Mrhl is crucial for spermatogonial division and differentiation [33]. Further studies are needed in gene-knocked-out mice to define the regulation of Mrhl in spermatogenesis.

Male infertility is often caused by maturation arrest (MA). *HongrES2* is a 1588-nt-long lncRNA co-transcribed by rats' chromosome 5 and 9 and expressed in testes; its expression in rates increases at the end of the first phase of spermatogenesis and reached a plateau at around day 450. Space-time specificity of this expression is manifested in the spermatogenesis. *Mil-HongrES2,* the spliced *HongrES2,* can down regulate the expression of *CES7,* the products of which affects capacitation. Nuclei weakly express mil-HongrES2, but strongly express HongrES2, indicating a splicing mechanism exists. Therefore, HongrES2 can regulate the maturation of sperms. Besides, the over expression of mil-HongrES2 can weaken spermatic capacitation, indicating lowly expressed endogenic HongrES2 promotes spermatic development [34]. Narcolepsy candidate-region 1 gene (NLC1-C) is a cytoplasmic lncRNA expressed in spermatogonia and early-stage spermatocytes. NLC1-C over expression promotes cell growth, whereas its low expression inhibits cell growth and accelerates apoptosis. Microarray analysis finds NLC1-C expression in MA patients is lower than in normal persons. NLC1-C is also bind to the RNA-binding domain of nucleolin, which inhibits the transcription of miR-320a and miR-383 and induces the proliferation of spermatogonia and early-stage spermatocytes in MA patients [35]. Results from a study of Liu *et al* provided a catalog of chicken testis lncRNAs. In total, 2,597 lncRNAs were identified in the chicken testis, including 1,267 lincRNAs, 975 antisense lncRNAs, and 355 intronic lncRNAs. They shared similar features with previous studies. Of these lncRNAs, 124 were differentially expressed. Among 17,690 mRNAs detected in this study, 544 were differentially expressed, including a bunch of genes affecting sperm motility [36]. Integrating analysis of lncRNA and mRNA LncRNAs expression in spermatogenesis listed in **Table 1** and see **Figure 3**.

### LncRNA PCAT1, SChLAP1, MALAT-1, PCGEM1 expression in prostate tumors

Prostate cancer (PCa), a malignant cancer of male reproductive system, is highly invasive and deadly. Though some knowledge is available about its genomic characteristics and epi-

genetic variations, the phathogenesis of PCa remains subtle. Until now, all the specific lncRNAs of PCa wait to be explored.

*PCAT1 and SCh LAP1*

Prostate cancer-associated transcript 1 (PCAT1), located in chromosome 8q24 and having a length of 2.0 kb, is specifically expressed, or only highly-expressed, in the prostate cancer [37]. According to Prensner, PCAT1 promotes the proliferation of cancer cells and participates in PCa metastasis, through a mechanism involving PRC2 and cMYC protein. PCAT1 may prompt the cancer development through inhibiting the expression of breast cancer susceptibility gene 2 (BRCA2) [38]. The high expression of SCh LAP1, a novel lncRNA found by Rohit Mehra, is associated with PCa development. Cox single/multiple-factor regression analyses display that the expression of Sch LAP1 is also related to the poor prognosis of PCa patients. So, SCh LAP1 can be taken as biomarker for the prognosis of radical prostatectomy [39].

*MALAT-1 and PCGEM1*

Results from a study of Ren et al. have shown that MALAT-1 is highly expressed in PCa tissues and cells, and this expression level is positively correlated with the GS score, PSA level and cancer stage. After the silencing of MALAT-1, the ability of PCa cell's multiplication, migration and invasion significantly falls. And the cell cycle is arrested at Go/G1. Besides, MALAT-1 shows its specificity in the core of the nucleosome. Through clustering, modifying, storing and processing mRNA in this region, MALAT-1 regulates the mutation of PCa genes and triggers its outbreak [40].

In addition, the knockout of HOTAIR slows down the multiplication, migration and invasion of PCa cells, and induces their apoptosis and cycle arrest. In this process, HOTAIR, as a target of miR-34a, inhibits the development of PCa. PCGEM1 has been proved as a type of PCa-associated lncRNA, for the fact that its expression significantly increases in PCa. The over expression of PCGEM1 can lead to the multiplication of PCa cells, making it a more promising biomarker than PSA [41]. LncRNAs expression in prostate tumors is shown in **Table 1** and **Figure 3**.

**LncRNAsGtl2, Neat1, AK124742, LncRNA274 expression in female reproduction**

*LncRNA Gtl2*

Recent studies reveal that lncRNAs (including Gtl2) from Dlk1-Dio3 region are positively correlated with the pluripotency of iPS cells. To uncover the spatiotemporal expression patterns and changes of lncRNA Gtl2, Yu Changwei et al analyzed the mechanism of Gtl2 epigenetic regulation. No changes of IG-DMR and Gtl2-DMR expression were found before and after lncRNA Gtl2 expression, which suggested its activation was not regulated by two DMRs' DNA methylation. So Yu Changwei et al checked the histone modifications in the promoter regions. They chose H3k9me3, H3K27me3, H3K4me3 and H3ac to perform the micro ChIP assay with a micro ChIP method published on nature protocols, and found lncRNA expression rose as H3K4me3 increased and developed from 8-cell stage to blastocyst.

Yu Changwei *et al* also studied the functions of lncRNA Gtl2 in preimplantation development. They knocked down lncRNA Gtl2 by shRNA lentiviral particle microinjection. Although about 60% of *Gtl2* was knocked down, the blastocyst formation rate did not change compared to the control group. However, interference of *Gtl2* compromised the outgrowth of both TE (trophoblast cell) and ICM (inner cell mass), and down regulated the adjacent genes from *Dlk1-Dio3* imprinted region and some stem cell pluripotency factors [42]. Expression profile analysis revealed that lncRNAs expression changed in different stages of human embryos and different time of mouse embryos. Weighted gene co-expression network analysis suggested that lncRNAs involved in human early-stage embryonic development were associated with oocyte maturation, zygotic genome activation and mitochondrial functions. Results from a study of Jia-jun Qiu *et al* showed that the network of lncRNAs involved in zygotic genome activation was highly preserved in human and mouse embryos, whereas in other stages no strong correlation was observed [43].

*Neat1*

Neat1, a non-protein-coding RNA. Shinichi Nakagawa found that Neat1-knocked-out mice with normal ovulation were stochastically infer-

tile and unilateral transplantation of wild type ovaries or progesterone changed the phenotype, suggesting that corpus luteum dysfunction and low-level progesterone were the primary causes of decreased fertility. Despite faint expression in most adult tissues, Neat1 was highly expressed in corpus luteum. However, luteal tissues were severely impaired in nearly half Neat1-knocked-out mice. These observations suggested that Neat1 is essential for corpus luteum formation and the pregnancy under a suboptimal condition [44].

*AK124742 and lncRNA274*

Another study found that AK124742 and PSMD6 expression levels in cumulus cells of high-quality embryo group were significantly higher than those in poor-quality group, which may affect oocyte maturation and embryonic development. The expression of mRNA PSMD6 was positively correlated with that of lncRNA AK124742 in cumulus cells, indicating that AK124742 may regulate the expression of PSMD6. Therefore, the expression levels of AK124742 and PSMD6 in human cumulus cells may be biomarkers to predict pregnancy outcome [45].

Ovary, a major female reproductive organ, functions in two ways: first, it produces oocytes and provides them a base to develop and mature; second, it secretes ovarian steroid hormones to regulate follicular development and reproductive cycle. Ovary development is regulated by multiple factors, such as gonadotropins, cytokines, and small nucleic acids. A study by Li Jiayu *et al* found 9 lncRNAs were relatively highly expressed in multiple mouse tissues by q PCR, and lncRNA647, lncR147 and lncRNA274 were specifically highly expressed in ovary at 8 weeks and metaestrus. The over expression of lncRNA274, and genes for follicular development were elevated and the number of ovulation increased after in vivo transfection. Transgenic mice with lncRNA274 as target gene were established. According the phenotype analysis, the number of offsprings significantly increased. These experimental results demonstrated that lncRNA274 could promote ovulation [46]. Rosalia Battaglia et al found 41 long non-coding RNAs could interact with oocyte microRNAs and may regulate folliculogenesis. These findings are important in both basic reproductive research and clinical application [47].

*H19*

Yao Ma *et al* analyzed the over expression of H19 in human trophoblasts and detected the cell proliferation with CCK-8 technology. Then the invasive ability of H19 in human trophoblasts was examined with Matrix Reagent through trans well method. RT-PCR showed lncRNA-H19 was highly expressed in human villous tissues from early spontaneous abortion patients and in human villous tissues from induced-abortion patients. Also up-regulation of lncRNA-H19 inhibited the cell proliferation in HTR8/SV neo-trophoblasts over expression of lnc RNA-H19 showed decreased motility in HTR8/SVneo trophoblasts. LncRNA-H19 inhibited early placenta growth and early vegetative layer cells, which could lead to early spontaneous abortion [48, 49]. LncRNAs expression in female reproductive diseases is shown in **Table 1** and **Figure 3**.

**LncRNAs XIST, H19, MALAT1, HOTAIR expression in female reproductive tumors**

For their roles in cell proliferation, differentiation, and apoptosis, lncRNAs are focused in the research on genesis of cancers or cancer subtypes. Also, their differential expression shows difference in different tumor stages [50, 51].

*LncRNA XIST*

Engreitz et al found that mouse lncRNA XIST (Inactive Specific Transcript) inactivating X-chromosome was transferred from its transcription site to distant region on the X chromosome. XIST, initially in the periphery of active genes on the X chromosome, gradually spreads across the genes with its a-repeat domain, to be bound with inactive X chromosome in differentiated female cells [52]. XIST encodes a spliced lncRNA with a unique characteristic from an inactive X chromosome. A study compared the total RNA expression profiles of primary and recurrent ovarian tumors from the same patient. The results showed that XIST was the most differentially expressed gene and down-regulated in the recurrent tumor. In addition, in vitro studies showed that the expression of XIST was correlated with Taxol sensitivity. The loss of inactive X-chromosome leads to the loss of XIST transcripts in ovarian cancer cell lines. The down-regulation of XIST causes the up-regulation of X-linked apoptotic inhibitor,

a mechanism that prevents drug-induced apoptosis and brings resistant phenotypes of cancer cells [53].

*H19*

A recent in vivo study has shown the co-expression between oncogenes and H19 in both primary human ovarian and endometrial cancers, confirming the existence of H19/let-7-dependent regulation. The anti-diabetic drug, metformin, can suppress the tumor cell migration and invasion, partly by epigenetic down regulation of H19 [54]. The loss of H19 imprinting has been detected in malignant serous cystadenocarcinomas. H19 is also up-regulated in most ovarian cancer tissues compared with adjacent non-tumor samples, which indicates a significantly positive correlation between its expression and tumor development. Cooperated with histone H1.3 over expression, H19 knockdown inhibits the growth and clonogenicity of epithelial ovarian cancer cells [55]. Literatures have revealed that the silencing of H19 induces cell apoptosis and cell cycle arrest at the G2/M phase. H19 RNA has been detected in a majority of patients with ovarian cancer ascites fluid [56]. H19 is over expressed in ovarian carcinomas, a result of expressed pro-metastatic genes [57]. Inovarian cancer cells, H19 over expression enhances their migration and invasion [58]. In addition, H19 sequestering of let-7 is required for H19 to function in EMT processes such as cell invasion and migration in ovarian cancer and uterine serous carcinoma cell lines [59]. H19 expression levels increase throughout endometrial epithelium tumorigenesis. Level of H19 expression is low in normal endometrial epithelium, but high in hyperplastic endometrium, especially in endometrial carcinoma and tumor tissue dedifferentiated tumor tissues. Furthermore, in cervical cancer, markedly increased levels of IGF2 expression and decreased levels of H19 expression were reported. However, the mechanism promoting this dysregulation is still unclear and needs to be further investigated [60].

*HOTAIR*

HOTAIR (Hox transcript antisense RNA), a long intervening non-coding RNA (lincRNA) transcribed from HOXC, is involved in epigenetic regulation, cooperative with polycomb repressive complex 2 and required for histone H3 lysine-27 trimethylation of the HOXD. The expression of HOTAIR is associated with cancer cell invasion and metastasis [61]. Also, its expression is higher in ovarian cancer stem cell (CSCs) than in non-CSCs [62]. Hazard ratios (HRs) of lncRNAs in cervical cancer patients show that HOTAIR generates the highest HR of 5.28. HOTAIR increases in a variety of human cancers [63]. Meanwhile, HOTAIR is a tumorigenic factor and can be adopted as a diagnosing or predictive biomarker in various cancer types [64]. HOTAIR is the most investigated lncRNA in cervical cancer. Hopefully, it can be used as a new biomarker in diagnosing and treating cervical cancer.

Moreover, in several ovarian cancer cell lines, the expression of HOTAIR causes resistance to cisplatin through wnt/β-catenin pathway activation [65]. In cervical cancer, VEGF and MMP-9 expression are up-regulated by HOTAIR. These two factors increase the migration and invasion of the tumor. HOTAIR is also correlated with recurrence of cervical cancer [66].

*MALAT1*

As one of the first identified cancer-associated lncRNAs, MALAT1 (metastasis-associated lung adenocarcinoma transcript) acts in the pathogenesis of different tumors, including hepatocellular carcinoma, cervical cancer, breast cancer, and colorectal cancer [67]. MALAT1 knockdown can suppress the proliferation, invasion and metastasis of human osteosarcoma cells. MALAT1 is mediated through PI3K/AKT signaling pathway. In addition, the expression of MALAT1 increases in primary metastatic bladder tumors, but not in non-metastasized tumors. Its silencing can result in a decrease in the epithelial-mesenchymal-transition (EMT)-associated ZincFinger E-Box Binding (ZEB) 1 and 2, and Slug levels, as well as an increase in the E-cadherin levels in bladder cancer cells. MALAT1 in EMT enhancement activates the Wnt signaling [68]. Although its mechanism in ovarian cancer is unclear, it is differently expressed in cells of metastatic ovarian cancers [69]. Qi Wen Chuan et al found that lowering the expression of MALAT1 in Hela cells could effectively reduce cell proliferation and migration [70].

MALAT1 is also over expressed in SKOV3ip, an ovarian cancer cell line derived from SKOV3

with a more metastatic phenotype. Furthermore, MALAT1 inhibition markedly suppresses tumorigenicity in SKOV3 ovarian cancer cells and changes the expression of several genes that are involved in cell proliferation, metastasis and apoptosis. However, the mechanism in this situation is still unclear and requires more detailed evaluation [71]. In addition, high levels of MALAT1 have been reported in endometrioid endometrial cancer [72], in relation with aberrant activation of the wnt/beta-catenin pathway where the wnt-effector transcription factor TCF4 interacts with the MALAT1 promoter region. This wnt/beta catenin aberrant activation is caused by the expression loss of the tumor suppressor PCDH10 which represses Wnt/beta-catenin activation [73]. Additionally, higher levels of MALAT1 are found in cervical cancer tissues and associated with a poor prognosis. MALAT1 is over expressed in the cervical cancer CaSki cell line, which promotes the cell growth and invasion and decreases its apoptosis [74, 75] (**Table 1** and **Figure 3**). LncRNAs-expressed female reproductive tumor disease (**Table 1** and see **Figure 3**).

## Conclusion and future perspectives

Advances in genomics and molecular biology have led to discovery of a large group of previous uncharacterized lncRNAs. Whether all of these transcripts are functional remains to be elucidated, but emerging evidence indicates that many lncRNAs play roles in multiple biological processes and that dysregulation of lncRNAs is often associated with reproductive diseases. Compared with miRNAs, lncRNAs are less conservative with overlapped functional domains. They act differently, as decoy molecules, guide molecules, or scaffold molecules that are all engaged in expression.

As a form of epigenetic regulation, lncRNAs may function in female reproductive processes through histone modification and chromatin reconstruction.

Different expression of lncRNA124742, lnc RNA Gtl2, lnc RNA-H19 and lnc RNA ENST00000-502521, Neat1, PCAT1, SChLAP1, Mrhl, and HongrES2 build up a regulatory system in reproductive diseases, providing us a new way into the reproductive disorders.

LncRNA expression profiling should be assessed in each cancer type as the most altered lncRNAs are different in cancers. Additionally, they may facilitate differentiation between different cancer histologic subtypes due to difference in expression pattern among different subtypes.

Further studies are needed to understand the roles of lncRNAs in reproductive diseases. With new technologies and searchable databases, such as bioinformatics tools and ontology databases, lncRNAs may give us a new perspective to diagnosis, prevent and treatment some reproductive diseases.

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## Disclosure of conflict of interest

None.

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